REMARKS

Claims 1, 2, 6, 15, 19, 36, 38, 41, 47, 53, 54, 56, 60, 62, 64, 66, 68, 69, 71, 72, 75, 76, 79, 86, 90, 97, 101, 105, 108, 113, 119 and 122-137 were pending. Claims 15, 19, 54, 56, 60, 62, 64, 66, 76, 127, 132, 133 and 137 have been amended. Claims 1, 2, 6, 36, 38, 47, 53, 68, 69, 71, 72, 75, 79, 86, 90, 97, 101, 105, 108, 113, 119 have been cancelled herewith as non-elected claims. Claims 135 and 136 have been canceled as duplicates of claims 64 and 66. Claims 15, 19, 41, 54, 56, 60, 62, 64, 66 and 76, 122-134 and 137 are pending.

Applicant also has amended the specification to correct a typographical error in the formula for SSC on page 15, to remove browser-executable code (hyperlinks) on page 16, and to update the Sequence Listing in view of the amendment to claim 56.

No new matter has been added.

Objection to the Specification

The Examiner objected to the presence of executable code (hyperlinks) on page 16, lines 14 and 15. Applicant has amended the specification to remove the hyperlinks text.

Claim Objections

The Examiner objected to claims 135 and 136 as substantial duplicates of claims 64 and 66, respectively. Applicant has canceled claims 135 and 136, and accordingly requests that the objection be withdrawn.

The Examiner objected to claim 60 as referring to "claims 64". Applicant notes that claim 60 did refer to "claims 54"; appropriate correction has been made. Applicant respectfully requests withdrawal of the rejection.

The Examiner objected to claims 15, 19, 62, 122, 123, 125-127 and 129 as drawn in part to a non-elected invention. Applicant has amended claims 15 and 19 to clarify that the agent is a nucleic acid agent. Withdrawal of the objection is respectfully requested.

Rejections Under 35 U.S.C. § 101

The Examiner rejected claims 60, 62, 63, 64, 66, 135 and 136 under 35 U.S.C. § 101 as directed to non-statutory subject matter. Claims 63, 135 and 136 were canceled. Claims 60, 62, 64, 66 and 132 have been amended to recite that the expression vectors or host cells are isolated. Accordingly, Applicant requests withdrawal of the rejection made under 35 U.S.C. § 101.

Rejections Under 35 U.S.C. § 112, Second Paragraph

The Examiner maintained the rejection of claim 56 under 35 U.S.C. § 112, second paragraph, as indefinite. Applicant has amended claim 56 to recite that part (b) refers to full length complements, and to make reference to the sequence of GenBank accession number AI024421 at the time the application was filed as SEQ ID NO:33.

Applicant also has amended claim 56 to have a minimum fragment size of 8 nucleotides. Support for this amendment is found in original claim 58 (now canceled but equivalent to claim 133). Claim 133 has been amended correspondingly to remove the 8 nucleotide limitation now present in amended claim 56. Accordingly, Applicant respectfully requests that the Examiner withdraw the indefiniteness rejection.

The Examiner rejected claims 63, 76 and 137 under 35 U.S.C. § 112, second paragraph, as indefinite.

Applicant canceled claim 63 in a previous amendment, and accordingly request that the rejection of claim 63 be withdrawn.

Claim 76 was rejected for the recitation of contiguous segments as non-overlapping. Applicant has amended claim 76 to clarify that the pair of isolated nucleic acid molecules do not overlap each other.

Claim 137 was rejected for the recitation of "constructed and arranged". Applicant has amended claim 137 to remove this recitation.

In view of the amendments and arguments presented above, Applicants respectfully request reconsideration of the rejections made under 35 U.S.C. § 112, second paragraph.

Rejections Under 35 U.S.C. § 112, First Paragraph

The Examiner rejected claims 15, 19, 41, 56, 62, 76, 122-134 and 137 under 35 U.S.C. § 112, first paragraph, for lack of an adequate written description.

(A) New matter rejections

Claim 56 was rejected as drawn to new matter for recitation of a GenBank accession number. This claim has been amended to add SEQ ID NO:33, representing the sequence corresponding to GenBank accession number AI024421. Applicant notes that the GenBank entry has not been modified since the filing of the instant application (the last and only modification of this EST sequence was made August 27, 1998). Accordingly no new matter is added by this amendment. Applicant therefore respectfully requests withdrawal of the rejection.

Claim 137 was rejected because the Examiner believes that the claim is drawn to encompass nucleic acids outside of Group 3 nucleic acids as were claimed in original claim 78, Applicants respectfully traverse the rejection.

First, Applicant notes that SEQ ID NO:23 was specifically identified as an embodiment of the invention in the Summary of the Invention section of the specification. On page 12, lines 7-9 of the specification, Applicant stated: "In each of the foregoing embodiments, a preferred nucleic acid molecule include [sic] the nucleotide sequence of SEQ ID NO:23 or fragments thereof, and polypeptides comprise SEQ ID NO:24 or fragments thereof, or are encoded by SEQ ID NO:23 or fragments thereof."

Second, NA Group 3 is a subset of NA Group 1. Applicant maintains that asserts that SEQ ID NO:23 is a member of both NA Group 1 and NA Group 3, as it is in Applicant's view a previously unknown nucleic acid coding for a cancer associated antigen precursor.

Therefore, Applicant's specific recitation of SEQ ID NO:23 in claim 137, which recitation was made in accordance with the species election requirement of the Examiner, does not introduce new matter. Applicant respectfully requests withdrawal of the rejection.

(B) Inadequate written description rejections

The Examiner rejected claims 15, 41 and 76, and claims dependent thereon, as lacking an adequate written description. Applicant has amended these three claims to recite specific stringent hybridization conditions as provided in the specification on page 15. Applicant also amended claim 127 (dependent from claim 15) to refer to the hybridization conditions now provided in claim 15. Accordingly, Applicant requests that the Examiner withdraw the rejection of claims 15, 41 and 76, and claims dependent thereon, as lacking an adequate written description.

The Examiner rejected claims 15, 19, 41, 60, 62, 64, 66, 122-132 and 135-137 under 35 U.S.C. § 112, first paragraph, for lack of enablement. Claims 60, 62, 64 and 66 have been amended to recite that the claimed vectors or host cells are isolated; this amendment is believed to obviate the instant rejection. Claims 135 and 136 have been canceled, rendering their rejection moot. Claim 137 is drawn to a kit for detecting the presence of the expression of a cancer associated antigen precursor; Applicant believes that the rejection of this claim was made in error, as it is not drawn to gene therapy or nucleic acids that encode a polypeptide that evoke an efficacious response to cancer.

(A) Gene therapy rejections

The Examiner rejected the claims because the specification allegedly does not teach one of ordinary skill in the art "how to overcome problems with in vivo delivery and expression with respect to the administration of the claimed nucleic acids or viral vectors comprising said nucleic acids." Applicant disagrees with this conclusion, particularly because the person of skill in the art is highly skilled and would exert only routine experimentation to use the claimed compositions; furthermore, the references relied on by the Examiner were published in 1995, 1996 and 1997 and therefore do not necessarily reflect the state of the art at the time of filing (2000).

Nevertheless, Applicant has amended the claims in order to facilitate allowance. Specifically, claims 15 and 41 have been amended to clarify that the compositions are for use in ex vivo therapies. The references cited by the Examiner (e.g., Orkin, see paragraph bridging pages 9 and 10 of the Office Action) and the specification (e.g., page 43) support the use of the claimed compositions in ex vivo therapy.

Accordingly, Applicant respectfully requests that the Examiner withdraw the rejection as it relates to gene therapy.

(B) Efficacious response rejections

The Examiner rejected the claims because the prior art allegedly teaches that tumor immunotherapy is unpredictable. Applicant respectfully traverses the rejection.

The Examiner cites the Apostolopoulos et al. reference (Nature Med. 4:315-320, 1998) for its teaching that an endogenous antibody response at the time of tumor peptide administration reroutes the immune response from a cellular to a humoral immune response. Although the Examiner acknowledges that this references teaches the use of a MUC1 peptide, the Examiner also notes that the references teaches that the reported findings "have implication for other immunotherapy approaches." Office Action at page 11. Applicant notes that Apostolopoulos is not quite so certain about the application of its findings, as it stated that the findings "may be relevant" to other immunotherapies. See page 318, lines 4-8 of the Discussion section, cited by the Examiner. Therefore, while Apostolopoulos teaches that there may be rerouting of the immune response, it does not teach the general applicability of the findings as suggested by the Examiner.

Moreover, Apostolopoulos teaches a means to overcome the immune response deviation, by targeting antigen-presenting cells in vitro followed by adoptive transfer (i.e., ex vivo therapy). When this therapeutic approach was taken by Apostolopoulos, the immune response was the same in animals having or lacking an endogenous antibody response. Because this technique was known at the time of filing of the instant application, one of ordinary skill in the art would know that it could be used if the situation favored it, i.e., if a patient had a pre-existing antibody immune response. Therefore, rather than supporting unpredictability of tumor immunotherapy,

Apostolopoulos in fact supports that one of ordinary skill in the art was enabled at the time of filing to perform tumor immunotherapy, including the use of the claimed compositions

The Examiner next cites Jager et al. (PNAS 97: 12198-12203, 2000) as supporting the conclusions of Apostolopoulos. Applicant disagrees that Jager supports the conclusions attributed to Apostolopoulos by the Examiner. While Jager indicates that the response to tumor peptide immunization differed in subjects having or lacking an antibody response to NY-ESO-1, Jager also clearly stated that the immunotherapy was effective in subjects having a pre-existing antibody response to the protein. Jager reported that 3 of 5 antibody-positive patients demonstrated stabilization of disease and regression of metastases. Therefore, the presence of antibody production by a subject does not mean *a priori* that the claimed compositions would be ineffective; Jager clearly refutes any such conclusion.

Further, in drawing conclusions about the teachings of Apostolopoulos and Jager, the Examiner states (top of page 12 of the Office Action) that induction of a CTL response is unpredictable. Applicant notes that a CTL response is not required by the claims. Rather, the claimed invention relates to compositions that increase MHC-cancer associated antigen complexes, or encode polypeptides that bind MHC to form complexes recognized by autologous antibodies or lymphocytes.

The Examiner also notes (Office Action, page 12) that tumors can be heterogeneous with respect to MHC presentation, and that the effect of the claimed compositions has not been demonstrated. Respectfully, Applicant should not have to provide human clinical trial data to enable the invention. The invention is the identification of a novel cancer-testis antigen OY-TES-1 (SEQ ID NO:23), and the demonstration of the expression OY-TES-1 in various tumors. The use of the novel sequences in particular immunotherapies must be viewed in the context of the knowledge and expertise of the art; in this art, the person of skill is highly skilled and possesses knowledge of tumor biology. Applicant notes that heterogeneity of MHC presentation has not presented an obstacle for those of skill in the art, as evidenced by the number of therapeutics in development for provoking an immune response against tumors.

The Examiner also noted that T cells that recognize self-antigens are subject to clonal deletion in the thymus. Applicant reminds the Examiner that SEQ ID NO:23 encodes a testis-specific protein that is expressed in testis (an immune privileged tissue) and in cancers as disclosed in the specification, not a self antigen that is widely expressed in normal tissue.

Therefore, clonal deletion of T cells specific for the OY-TES-1 protein would not be expected to occur.

The Examiner cites several references supporting the clonal deletion of T cells that are directed against normal or self antigens (Lauritzen et al., Sarma et al., Ohlen et al.). None of these references considered Applicant's situation, which involves a cancer-testis antigen. In this respect, the Jager et al. reference cited by the Examiner has far greater similarities than the cited references, as it demonstrates that an effective immune response can be stimulated in the context of a cancer-testis antigen (NY-ESO-1).

The Antoinia et al. reference points out the differences between CTL activity *in vitro* and *in vivo*. While it may be the case for the DAGE antigen, this one paper does not suggest that one of ordinary skill in the art would not be enabled to make and use the claimed invention; it simply stands for the proposition that CTLs recognizing the DAGE antigen (or at least one peptide thereof) do not effectively lyse tumor cells. As previously noted, the Jager et al. reference would suggest that the result of Antoinia et al is not indicative of the results obtainable with all tumor antigens.

Regarding the suggestion made by the Examiner that certain tumors may elicit tolerance, it is difficult to believe that one of ordinary skill in the art would take this data to mean that only large numbers of slowly growing tumor cells, or small numbers of rapidly growing tumor cells, would not be subject to host tolerance. Nevertheless, even if one were to assume that the Examiner's assertion is correct, it is not proper to reject claims for lack of enablement because there may be some inoperative embodiments encompassed within the scope of a claim. The Paul textbook does not provide information about tolerance in the context of immune response enhancement as would be provided by the use of the claimed compositions.

The Examiner suggests on page 15 of the Office Action that it cannot be predicted that all patients having cancer expressing the polypeptide encoded by SEQ ID NO:23 would have T cell repertoires that would include a T cell specific for this antigen (which Applicant notes is a cancer-testis antigen, not a "self" antigen as that term is generally used). While it is true that the contents of a person's T cell repertoire cannot be predicted *a priori*, it is nevertheless also true that T cell repertoires for any subject include T cells that will recognize presented antigens with some affinity that can be expected to be efficacious. The situation presented is analogous to vaccination with an infectious disease agent; as an example, consider smallpox vaccination.

Smallpox infection is considered to be absent worldwide. Certainly in the United States, a person administered a smallpox vaccine would be considered to lack T cells specific for smallpox antigens in the sense that this term is used by the Examiner. Nevertheless, a person so vaccinated would very likely have lymphocytes that recognize the vaccine antigen, and the vaccine would therefore stimulate an immune response. The same can be said for any infectious disease that a subject has not been exposed to. Therefore, the lack of a "specific" T cell for OY-TES-1 would not be an obstacle for mounting an immune response, because one or more T cells that recognize the antigen by TCR binding of antigen presented by an APC would be present in the subject.

The Examiner's suggestion on page 15 that one of ordinary skill in the art would be forced to conduct undue experimentation absent "a demonstration that the administration of the claimed polypeptides or cells expressing said polypeptides overcomes immunosuppression in the host, the rapid growth of tumor cells, failure to access the tumor...and objective evidence that the target tumor cells in vivo present adequate tumor rejection antigen on the surface of all the tumor cells". First, Applicant is not claiming prevention of cancer; the claimed invention can be used in reducing its occurrence and/or slowing its progression, as was described in the specification. Second, the Examiner's objections are based on mere possibilities of difficulties that are based on examples selected from the literature. These difficulties are not necessarily applicable to an immunological approach to the treatment of cancers expressing OY-TES-1. Third, a requirement for in vivo testing goes far beyond what is required to enable the claimed invention for one of ordinary skill in the art. The highly skilled artisan does not need clinical trial data to know how to make and use the claimed invention, based on the well known principles of immunology and tumor biology. Again, Applicant emphasizes that some experimentation is permissible, as long as the experimentation is not undue; in the instant case any experimentation that might be required is routine in this art.

Utilization of the claimed compositions requires no more than routine experimentation for those ordinary skill in the art. Therefore, even if there is some unpredictability in the field of the invention (which is less than alleged by the Examiner, based on a fair interpretation of the references as explained above), and given the teachings of the specification and the high level of skill in the art, any experimentation that might be required by the skilled artisan is not undue.

Regarding the recitation of nucleic acids in claims 15, 41 and 127, Applicant has amended the claims to clarify that the complements of nucleic acid molecules that hybridize to SEQ ID NO:23 are used in the claimed compositions. Applicant appreciates the Examiner's observation of the discrepancy in the claim as previously pending.

In view of the claim amendments and arguments presented above, Applicant respectfully requests that the Examiner withdraw the rejection as it relates to an efficacious response.

Rejections Under 35 U.S.C. § 102(b)

The Examiner rejected claims 15, 19, 41, 54, 56, 60, 62, 64, 66, 76 and 137 under 35 U.S.C. § 102(b) as being anticipated by Jacobs et al (WO 98/45437) as evidenced by GenBank accession number AAV88163.

After a diligent search, Applicant was unable to locate an entry for accession number AAV88163. By homology searching, Applicant identified a sequence matching that shown in the sequence comparison provided by the Examiner. This sequence has GenBank accession number BD060281. The identity of BD060281 and the AAV88163 sequence shown in the homology comparison provided by the Examiner were confirmed using the BLAST2SEQ tool found at the NCBI website.

Applicant asserts that Jacobs does not anticipate the claimed invention because it does not provide the required sequence. The differences between the Jacobs sequence and that claimed in the instant application are as follows. First, Jacobs provides a sequence that is an EST that does not encompass the coding sequence of SEQ ID NO:23. The Jacobs sequence, therefore, does not meet the requirement of the claims that the hybridizing sequence "codes for a cancer associated antigen precursor". Second, Applicant notes that the source of the Jacobs sequence reported at BD060281 is *Zea mays*, i.e., corn. Therefore, because the Jacobs sequence does not encode a cancer associated antigen precursor, as evidenced by its size relative to the coding region of SEQ ID NO:23 and because it is a sequence isolated from corn, Jacobs does not anticipate the claims.

The Examiner also rejected claims 54 and 56 under 35 U.S.C. § 102(b) as being anticipated by the random primer [5'd(NNNNNN)3'] set forth on page 91 of the 1993-1994 New England Biolabs, Inc. catalog.

The NEB random primer does not anticipate claim 54 for two reasons. First, claim 54 requires that the claimed nucleic acid molecule codes for a cancer associated antigen precursor. Second, claim 54 as amended sets forth specific high stringency hybridization conditions that exclude hybridization by the NEB random primer.

The NEB random primer does not anticipate claim 56 for the reason that the claim as amended recites that the fragment of SEQ ID NO:23 is at least 8 nucleotides in length.

Accordingly, in view of the claim amendments and reasoned statements above, Applicants respectfully request the Examiner reconsider and withdraw the rejections made under 35 U.S.C. § 102(b).

CONCLUSION

In view of the foregoing amendments and remarks, this application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this amendment, that the application is not in condition for allowance, the Examiner is requested to call the Applicant's attorney at the telephone number listed below.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,

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